Pediatric Surgery International (2019) 35:1035–1041
https://doi.org/10.1007/s00383-019-04502-4

REVIEW ARTICLE

Application of indocyanine green in pediatric surgery

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Accepted: 18 June 2019 / Published online: 26 June 2019

Abstract
The use of near-infrared (NIR) fluorescence imaging with indocyanine green (ICG) has gained popularity in many fields in adult surgery, such as sentinel lymph node mapping, intra-operative solid tumor identification, and organ perfusion assessment. However, the clinical application of ICG in pediatric surgery is just at the beginning. This review paper presents the advantages, current applications and potential developments of NIR fluorescence imaging with ICG in our field.

Keywords Indocyanine green · Fluorescence · MIS

Introduction

Technological advances such as high-quality computed tomography (CT) and magnetic resonance imaging have brought influential changes in the pre-operative planning in pediatric surgery. However, the translation of these pre-operative images to the surgical field can be difficult and may not always correspond to the operative findings. Indocyanine green (ICG), a fluorescent iodide dye, has come to light as a potential solution to the challenge. This dye has gained exponential attention in the practice of general surgery, but its use in pediatric surgery is still not fully clarified. Our unit has been utilizing ICG in our practice for the past 2 years and in this review, we will describe the current use and potential applications of ICG in pediatric surgery, based on our experience and others in the literature.

Overview of ICG

ICG is a water-soluble tricarbocyanine dye developed by Kodak Research Laboratories for near-infrared (NIR) photography in 1955 [1]. It was first approved by the Food and Drug Administration (FDA) in 1956 to study hepatic and cardiac functions in human [2]. ICG is excited when illuminated by NIR light with wavelength of 778–806 nm. The fluorescence emission is maximal at wavelength of 832 nm and can penetrate tissue up to 15 mm [3, 4]. This emitted light is then captured with special camera to be transformed and displayed as visible light.

ICG is injected intravenously and due to its protein-binding characteristic, majority of the plasma protein-bound ICG stays within the intravascular space. It is then almost exclusively metabolized by the liver and excreted into bile at a rate of 18–24% per minute. The half-life is shortest at around 3–4 min during the first 10–20 min after injection [5, 6]. Although the clearance rate decreases subsequently, it is cleared quickly enough to allow multiple injections in most procedures. The use of ICG is relatively safe: comparing to lethal dose up to 80 mg/kg, the standard dose of 2 mg/kg is basically nontoxic, with the exception of iodide allergy which is uncommon [7].

Initially, ICG was used to quantitatively measure hepatic and cardiac blood flow using the Fick principle. However, its value in the measurement of hepatic function was soon realized [8]. As ICG has high tendency to stay intravascular and is only excreted by liver, hepatocyte uptake is the rate-determining step in its clearance. Therefore, its clearance rate is a surrogate marker of overall liver function, which is affected by liver pathologies such as liver cirrhosis. The ICG retention value at 15 min (ICGR-15) was developed upon this concept and is now the gold standard liver function test before major hepatectomy [9].

Other than the hepatic function, ICG has also served in the cardiac counterpart. It has been used as an adjunct to echocardiograms, when the technological limitation of the

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time made it hard to differentiate the echoes produced by different heart chambers [10]. It was the intracardiac injection of ICG that aided the identification process, but with improvement in ultrasound quality its use in this context is no longer necessary.

It took more than 10 years before ICG was used to provide direct visualization of blood vessels, not just being focused on its blood levels, when its use was expanded to ophthalmology for retinal angiography [11]. This application truly revealed ICG potential to provide visual clues in clinical anatomy during surgical procedures, which laid the cornerstone for the concept of "image guided surgery".

Hepatobiliary surgery

Biliary atresia/Kasai operation

Intra-operative cholangiogram (IOC) is the gold standard for diagnosis of biliary atresia and is usually performed together with Kasai operation [12]. Conventionally, it involves the injection of radio-opaque contrast material into the gallbladder and observes the drainage of contrast in the biliary system. Hirayama et al. first reported their experience to use ICG as an alternative in 2015 [13]. ICG was injected on the day before the operation, and was observed with NIR camera during the operation. They were able to demonstrate the absence of fluorescence in the biliary tract and confirmed the diagnosis of biliary atresia during the operation (Fig. 1a, b). The author suggested that the use of ICG cholangiogram can better visualize the biliary flow of the hepatic duct at the porta hepatis before dissecting the fibrous cone, thus a more appropriate level and extent of dissection can be determined. Moreover, it can also be used to evaluate biliary excretion post-operatively by observing the fluorescence of the feces and compare it to the pre-operative value.

Laparoscopic cholecystectomy

Laparoscopic cholecystectomy is the treatment of choice for symptomatic gallstones and biliary dyskinesia, among other indications in children [14, 15]. The techniques and instruments used in children are similar to those used in adults, but more difficulty may be encountered in children with gallbladder disease, as anatomical variations are more common and the abdominal space is more limited due to the relatively larger livers. Thus, more care must be taken during dissection, especially around the Calot's triangle.

ICG can be a valuable tool in identifying the cystic duct and common bile duct (CBD) before the dissection of Calot's triangle, allowing for a more careful dissection with minimal risk of injury to either the biliary tree or blood vessels. Experience of laparoscopic cholecystectomy with ICG in adult showed a faster and more accurate visualization of the cystic duct and CBD, which helped to avoid unintentional bile duct injury [16]. This is particularly useful when the anatomy is difficult to identify, which may be the result of variation in biliary anatomy or history of severe inflammation, leading to injury of Calot's triangle and fibrotic gallbladder [17] (Fig. 2).

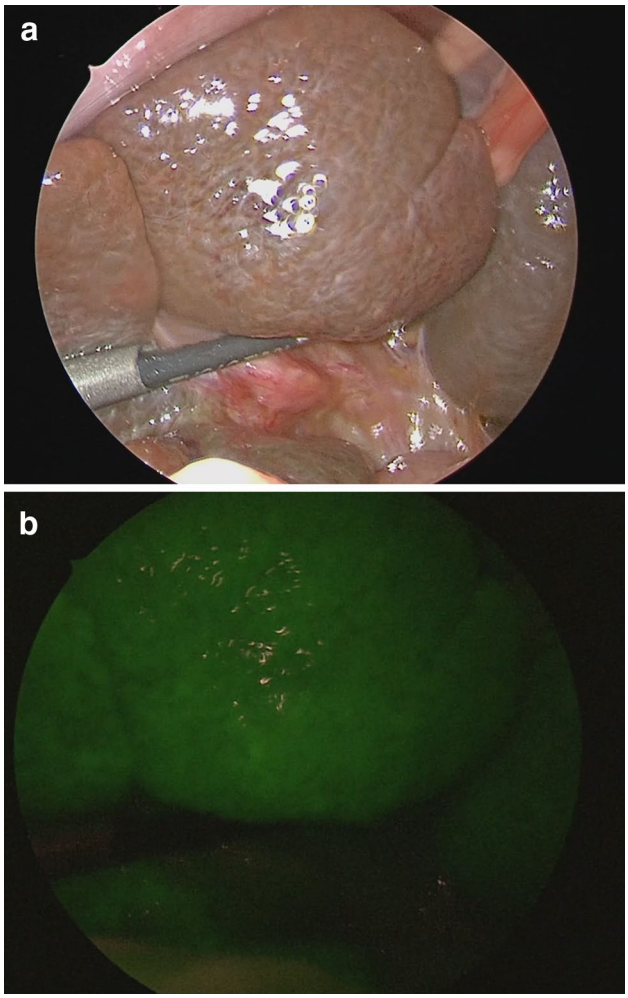

Fig. 1 Intra-operative image of the porta hepatis in a baby suspected to have biliary atresia: **a** under normal light; **b** image after ICG injection. Note the absence of fluorescent dye in the porta hepatis

IOC may be necessary during cholecystectomy if there is evidence of bile duct obstruction or bile duct injury. Osayi et al. have demonstrated that ICG imaging is a useful alternative to conventional IOC in 2015. Their study showed that performing ICG cholangiogram is not just only faster and cheaper, but also more convenient in the operation theater because the large fluoroscopy machine is not required [18]. When comparing to conventional IOC, ICG cholangiogram requires neither radiation nor dissection of the Calot's triangle. Furthermore, ICG cholangiogram only involves intra-operative intravenous injection of

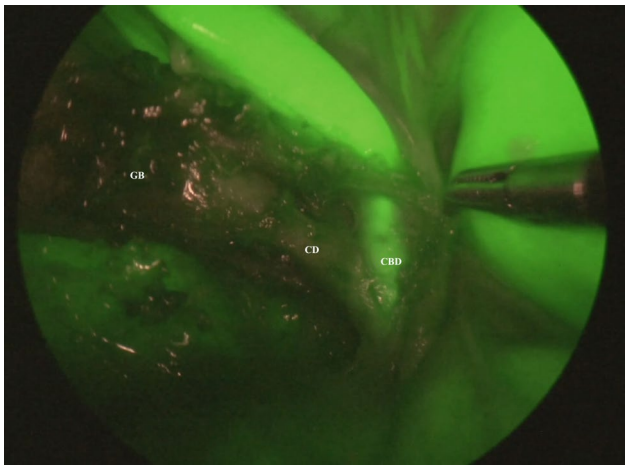

Fig. 2 Intra-operative photograph during laparoscopic cholecystectomy, with Calot's triangle shown clearly after ICG injection (*GB* gall bladder, *CD* cystic duct, *CBD* common bile duct)

ICG, whereas conventional IOC involves the insertion of a transcystic tube to inject contrast material, which has been reported as a cause of bile duct injury [19]. There are several limitations of ICG cholangiogram, including difficulty in identifying ductal stones and limited depth of penetration, which may not allow visualization of the biliary anatomy if covered by thickened tissue such as in obese patients or after severe inflammation [20]. However, all of these factors are less common in children.

Urology

Varicocele

Varicocele treatment is among one of the earliest applications of ICG in pediatric urology. Principle of treatment involves ligation of spermatic veins either via an inguinal or laparoscopic approach. Studies have previously reported the success of ICG use in both microsurgical subinguinal and laparoscopic artery sparing varicocelectomy in adults, as well as laparoscopic Palomo technique in children [21–23]. Laparoscopic varicocelectomy has been shown to be safe and efficient in children, and the Palomo technique in particular reports a lower operative failure rate, compared to other artery sparing procedures. Its major complication is post-operative hydrocele, occurring in up to 30% of patients [24]. However, there is no increased incidence of testicular hypertrophy or atrophy. Modification to the technique, including lymphatic sparing procedure using lymphography, has been proposed to reduce post-operative hydrocele.

Dyes such as isosulfan blue are currently used for lymphography in these procedures, but ICG may be a useful alternative with certain advantages over other dyes. According to Exposito et al., use of ICG in lymphography requires direct injection of ICG into the testes, after which the lymphatic vessels will appear fluorescent in NIR mode. A single injection is sufficient, as fluorescence starts 20–40 s after injection and can last for 15 min. Compared to current techniques, the direct injection of ICG into the testes is technically easier than the intradartoic injection required for isosulfan blue. In addition, isosulfan blue leaves a blue mark on the scrotum and causes blue urine for a few days post-operatively, as it is metabolized by the kidneys, whereas neither occurred in ICG use, which is metabolized by the liver. Although the blue color is harmless both on the scrotum and in urine, it is less preferable. The only disadvantage of ICG is the extra equipment required: a camera system with dual mode for fluorescent imaging as well as a laparoscope with a special filter. According to preliminary studies, ICG is successful in identifying lymphatic vessels and preventing post-operative hydrocele, as assessed at mid-term follow-up [25].

ICG can also be used to identify spermatic arteries in addition to lymphatic vessels. The preservation of arteries is important to some surgeons as mass ligation of both artery and vein may cause testicular atrophy, but attempts to selectively ligate the veins only will run the risk of leaving behind smaller veins, which is thought to be the cause of recurrent varicoceles in laparoscopic varicocelectomy. With the aid of ICG to visualize the arteries and veins, Tomita et al. reported a decrease in the incidence of varicoceles and hydroceles while significantly increasing fertility in their series [23]. This benefit is further supported by the higher sensitivity to identify testicular arteries than a pre-operative CT angiography in another series [22]. Although arteries and veins are easily distinguishable under ICG by observing the timing and direction of flow, a major limitation is that the non-fluorescent vessels could not be easily differentiated between a lymphatic vessels or veins that went into spasm. More research is still necessary to get a better understanding of ICG perfusion rate in different types of tissue and vessel (Fig. 3).

Duplex kidney

Duplex kidney is often associated with ectopic ureter and can be complicated with obstructive or reflux nephropathy, resulting in nonfunctioning kidney moiety. Heminephrectomy is usually offered to these patients to prevent recurrent urinary tract infection [26]. However, the dissection plane between the nonfunctioning and the normal moiety may not be well defined, and injury to the normal moiety can result in devastating complications [27, 28]. The advancement from open, through laparoscopic, until the recent use of robotic platform has not completely resolved the problem [29, 30].

Adult urologists had ample experience with applying ICG in performing partial nephrectomy [31–35]. But

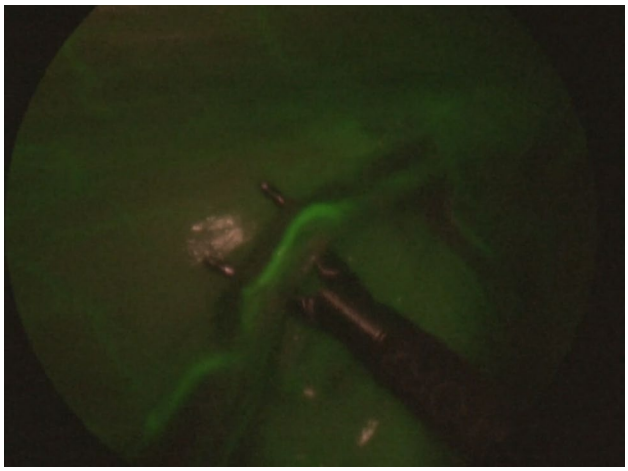

Fig. 3 Testicular artery highlighted after ICG injection during laparoscopic varicocelectomy

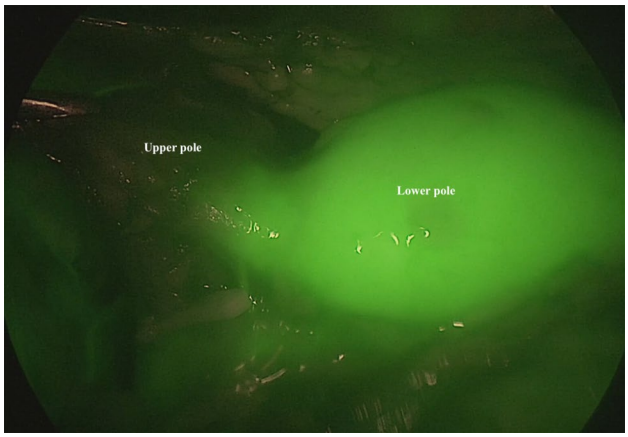

Fig. 4 Intra-operative photo during left upper pole nephrectomy. Absence of perfusion in the upper moiety after upper pole blood vessel ligation. Dissection plane for heminephrectomy demarcated

majority of these reports were about robotic surgery of renal tumor. Other than tumor localization, the use of ICG in finding the vascular territory may be more applicable to children in the context of duplex kidney [36–39]. As conventionally the arterial supply to the affected moiety was only determined by information from dissection alone, this could sometimes be misleading. Among the series of six children who underwent heminephrectomy for duplex kidney reported by Herz et al., one accident was avoided by ICG use which prevented inadvertent ligation of a normal moiety artery that appeared to be going into the affected moiety [40]. In addition to identifying the correct blood vessel for ligation, the use of ICG can also help to delineate the anatomical boundary or dissection plane between the two moieties, thus decreasing the risk of post-operative urinary leakage [41] (Fig. 4).

Oncology

Hepatoblastoma

Use of ICG in liver surgery has been well established in adults with hepatocellular carcinoma, but its use in the pediatric counterpart of hepatoblastoma was much less studied [42]. As surgical resection is the rule to achieve hepatoblastoma cure, ICG can also aid in pediatric hepatectomy by same principle. Although both normal hepatocytes and tumor cells can take up ICG, the mechanism behind this technology is due to the different excretion rate of the dye between the two cell types, in which hepatocytes can excrete ICG much faster. As a result, ICG will be retained inside tumor cells for a much longer time, and can produce fluorescence visualization under NIR imaging, in contrast to the washout appearance of normal liver parenchyma [43]. Surgeons can thus identify all lesions and perform resection with adequate margin under direct vision.

However, as ICG washout is dependent on the excretory function of the cells, the timing of the ICG injection is crucial. If the injection is too close to the time of surgery, some ICG may still be retained in normal liver tissue, leading to false-positive lesions. This is especially true of noncancerous liver tissue with poor function such as those with background of liver cirrhosis. Experience from adult patients with hepatocellular carcinoma have reported false-positive rate as high as 40% [44]. For hepatoblastoma patients in which liver cirrhosis is uncommon, our ICG injection time is at least 24 h before surgery. Some may still need to be injected at least 3–4 days prior to surgery to maximize the visual contrast and clearly assess the lesion [45].

Thoracic surgery

Congenital pulmonary airway malformation

Indications for thoracic surgery in pediatric patients include congenital pulmonary airway malformation (CPAM), pneumothorax, empyema and pectus excavatum. CPAM is probably the most common one, and its trend is rapidly rising [46]. In the literature, most published works about use of ICG in thoracic surgery were related to three categories: sentinel lymph node detection, planning for segmentectomy and tumor detection [47]. Lymph node metastasis is quite rare in the pre-malignant condition of CPAM so its use may be not very relevant, but the latter two applications are much more significant.

Although classically lobectomy is the gold standard to prevent residual lesion, segmentectomy is gaining

interest in the field for selected cases [48]. Identification of intersegmental plane can be difficult in infants, and less than perfect transaction can lead to prolonged air leak, retention of devascularized tissue and compromising the resection margin. Majority of authors who employed ICG to assist in plane identification would first ligate the main arterial supply to the target segment, followed by systemic injection of ICG [49–51]. On the other hand, Sekine et al. identified intersegmental plane by transbronchial injection of ICG into the targeted bronchioles, which then highlighted the segment of interest [52]. This method had the advantage of avoiding previous ligation of blood vessel and the systemic injection of ICG is not necessary. But this technique may not be always possible in infant as bronchoscope may be too large to go into bronchiole level. With the use of ICG, it is hoped that segmentectomy can be performed with greater precision in children.

Lung nodules

With improvement in availability and resolution of CT scan, detection of lung nodules is increasingly common while the nodule size is getting smaller. This often poses a diagnostic and therapeutic challenge to surgeons: diagnostically it is difficult to determine its significance, and therapeutically may not be able to locate the lesion for excision due to its small size. The golden rule is to palpate the lesion before excision, but in the era of thoracoscopy, lack of tactile sensation may be an issue.

Pre-operative hookwire marking of lung nodules is a well-established technique to tackle small nodules among adult thoracic surgeons. The use of "ICG tattoo" has recently become an interesting alternative [53]. The author injected a low dose of ICG to lung nodules under CT guidance, and NIR thoracoscopy was able detect all lesions except one deep-seated nodule which was almost 5 cm from the pleural surface. With this novel technique, the risk of dislodging hookwire during transfer from CT suite to operation theater is virtually eliminated, but risk of dye spillage and hence poor marking remains as of the conventional use with methylene blue.

Lung is the most common site for metastasis in patients with hepatoblastoma. As ICG is not taken up by the lung tissue while metastatic tumor cells can, this preferential uptake allows for clear detection of lung lesions. Souzaki et al. reported injecting ICG 24 h before operation, which showed lung metastasis was clearly seen in all cases [54]. This advantage may be enhanced further under thoracoscopic environment in which the background can be completely darkened to increase the visual contrast and hence the sensitivity of detecting lung lesions.

Limitations

ICG does have its limitations. Not to mention the special equipments required may not be available in all centers, the sensitivity and visibility of ICG are significantly affected by the depth of the lesion. It is also difficult to detect very small lesions if the intensity of fluorescence is too weak. On the other hand, one must note that ICG can accumulate in inflamed tissues, limiting the specificity of this contrast agent. Up till now most knowledge and data were generated from adult experience, making the dosage and timing of injection in children difficult to standardize.

Conclusion

ICG is safe and has many potential applications. It has demonstrated its usefulness in visualizing anatomy of biliary system, vascular territory in various organs, tissue perfusion and tumor localization. More research is needed to determine the true extent of ICG application in pediatric patients. Whether it is a complementary to or replacement of traditional methods is to be determined, but certainly this is a contrast agent with huge potential.

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